SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name: Automated Microscope and Imaging System

Device Trade Name: ThinPrep® Imaging System

Applicant's Name and Address: Cytyc Corporation
85 Swanson Road
Boxborough, Massachusetts 01719

Date of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P020002

Date of Notice of Approval to Applicant: June 6, 2003

II. INDICATIONS FOR USE

The Cytyc Corporation ThinPrep® Imaging System (hereinafter called the ThinPrep Imaging System) is indicated for assisting in primary cervical cancer screening of ThinPrep® Pap Test slides for the presence of atypical cells, cervical neoplasia, including its precursor lesions (Low Grade Squamous Intraepithelial Lesions, High Grade Squamous Intraepithelial Lesions, and carcinoma as well as all other cytologic criteria as defined by 2001 Bethesda System: Terminology for Reporting Results of Cervical Cytology. [1]

III. CONTRAINDICATIONS

There are no known contraindications for use.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the ThinPrep® Imaging System labeling (Attachment 1).

V. DEVICE DESCRIPTION

The ThinPrep Imaging System is an automated imaging and review system for use with ThinPrep Pap Test slides. It combines computer imaging technology to identify microscopic fields of diagnostic interest with automated stage movement of a microscope in order to locate these fields. In routine use, the ThinPrep Imaging System selects 22 fields of view for a cytotechnologist to review. Following review of these fields, the cytotechnologist will either complete the diagnosis if no abnormalities are identified or review the entire slide using the Autoscan feature if any abnormalities are identified. The ThinPrep Imaging System also allows the physical marking of locations of interest for the cytopathologist.

The operation and design of the ThinPrep Imaging System are grouped into two major functions. First, the ThinPrep Pap Test slide is analyzed by a computer controlled microscopic imaging device to locate the cells of interest. The *x* and *y* locations of these cells on the slide are saved in a database. Second, an automated reviewing microscope retrieves the locations of the cells of interest from the database and sequentially positions these locations for evaluation and interpretation by the cytotechnologist.

The two major subsystems are an Image Processor for computer-image analysis and a Review Scope providing automated microscope location.

The three principal components of the Image Processor are

(a) User Interface equipment that consists of the monitor, keyboard, and mouse. These are standard computer interface devices and are operated just as they are when used with a personal computer;

(b) Imaging Processor, a tabletop unit that contains the hardware used to image the cassettes of slides. This unit holds 10 cassettes and each cassette holds 25 slides. A Verification Slide is loaded when the Processor is installed in the laboratory and is used by the Image Processor to verify the proper functioning of the hardware and software; and

(c) Image Processor Controller with internal Server, which is the computer and software used to capture and analyze the slide images as well as store the results of the analysis. The Server is the central data manager for the ThinPrep Imaging System. As slides are imaged by the Image Processor and reviewed on the Review Scope, the Server stores, retrieves, and transmits information based on the slide ID.

The three components of the Review Scope are the

(a) Microscope with automated stage. The automatic slide movement presents the fields of view containing cells of interest previously selected by the imaging system to the reviewer. Manual review of the slide may also be performed. An automated marking system allows the reviewer to mark sites for further review; (b) Display Unit used to communicate with the reviewer; and (c) Pod used to control the microscope.

VI. ALTERNATIVE PRACTICES OR PROCEDURES

The primary procedure for screening conventional Pap smear and liquid-based Pap test slides is the cytotechnologist review of the entire slide using manual microscopy. In addition, there is one approved computer-assisted system, the Focal Point from TriPath Imaging, Inc., which is designed to select out up to 25% of slides that need no further review. The remaining slides are reviewed by a cytotechnologist using manual microscopy. An additional up to 15% of review slides are selected for quality control (QC) re-screening. The Focal Point is for use only with conventional Pap smear slides and SurePath liquid-based slides.

VII. MARKETING HISTORY

The ThinPrep Imaging System has not been marketed in the United States or any foreign country.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The ThinPrep Imaging System, when used to assist in the screening of slides for cervical cytology, poses no direct risk and only indirect risk to the patient. The indirect risks are associated with the device's ability to correctly determine the 22 fields most likely to contain abnormal cells. If the most significant fields are not selected for the cytotechnologist to review, this may result in false positive or false negative diagnoses.

False positive diagnoses may result when a slide is interpreted as containing abnormalities when no disease is present. As a result, the patient may have an unnecessary colposcopy exam, which is a noninvasive procedure or may be referred for a biopsy, which is an invasive procedure. False negative diagnoses may result when a slide is interpreted as containing no abnormalities when disease is actually present. This may result in delayed diagnosis or treatment for the patient.

IX. SUMMARY OF PRECLINICAL STUDIES

Preclinical Supporting Studies were designed to evaluate and verify the performance of the ThinPrep Imaging System.

1. "N" Study

The objective was to determine the relationship between the numbers of fields of view selected and reviewed with the ThinPrep Imaging System and the proportion of endocervical component and abnormal cells detected using the Bethesda System criteria.[2] Routine and referral specimens that were routinely processed at a hospital laboratory were prepared using the ThinPrep 2000 Processor and stained using the Cytyc ThinPrep Stain. Two cytotechnologists each reviewed 208 cervical cytology slides on a manual microscope and recorded their results (control).

The slides then were processed on the ThinPrep Imaging System and the top 30 objects of interest x/y coordinates were stored on five separate data disks. Each data disk identified the coordinates that allowed the cytotechnologist to move across the slide to the following number of microscopic fields of interest: disk #1 allowed review of 10 fields; disk #2, 15 fields; disk #3, 20 fields; disk #4, 25 fields; and disk #5, 30 fields. Using the automated microscope, the same two cytotechnologists, after a suitable washout period, reviewed the allowed number of fields for each disk. The first ThinPrep Imaging System review utilized an "n" of 20 fields (test) and this diagnosis was compared to the manual review of the slide (control). The success of using "n" number of fields was used to justify an increase or decrease in the number of fields by increments of five.

Cytotechnologist A missed 3/18 abnormal cases on manual review. With ThinPrep Imaging System, 2 cases were missed using 20 fields; 4 were missed with 15 fields; and 5 with 25 fields. Cytotechnologist B missed no cases of abnormality on manual review. With ThinPrep Imaging System, 1 case was missed using 20 fields; 3 were missed with 15 fields; and 2 with 25 fields. At both 20 and 25 fields, specimen adequacy results were similar to the manual review. Based on these results, 20 fields of view were selected as the desired "n". However, a "cluster" algorithm that identifies two additional fields of view was added to aid in the determination of abnormality and specimen adequacy bringing the total number of review fields to 22.

2. Analytical Cancer Study

The objective of this study was to challenge the ThinPrep Imaging System to see if at least one cancer cell or its precursor lesion would be selected in one of the 22 fields of view whether the slide contained many cancer cells or few cancer cells. Detection was based on the ability of the reviewer to detect at least one abnormal cell or cluster of cancer cells. The 33 ThinPrep Pap Test slides in this study were made from residual cervical specimens from biopsy confirmed cancer cases. Initially, a board-certified cytopathologist reviewed the entire slide using a microscope and reticle fitted with a grid. The cytopathologist moved the slide through the adjacent grids and counted the cancer cells in the entire cell spot. Cancer cells were identified according to the Bethesda 2001 criteria for Glandular Cancer, Squamous Cancer and Adenocarcinoma-in-situ. Single cells as well as cell clusters were counted.

The slides were processed on the ThinPrep Imaging System and reviewed by a cytotechnologist using the ThinPrep Imaging System Review Scope. Only cells in the 22 fields of view selected by the TIS were reviewed by the cytotechnologist. For each of the 22 fields of view, a cytotechnologist counted and recorded all abnormal cell types defined as ASCUS, LSIL, HSIL, Squamous Cancer, AGUS, AIS, and Glandular Cancer. All cells were identified as single cell or cell clusters.

Finally, the same cytopathologist used in the manual count of cancer cells reviewed the slides again using the Review Scope, looking at the 22 fields only. The cytopathologist counted the number of cancer cells and its precursors, HSIL, AGUS, or AIS cells present in these FOVs. The results are displayed in Table 1 below.

Table 1: Summary of Results From Analytical Cancer Study

Cytopathologist Full Manual Review	Cytotechnologist Review of Imager Identified 22 Fields of View *	Cytopathologist Review of Imager Identified 22 Fields of View **
10 Glandular Cancer	5 Glandular Carcinoma 1 Squamous Cell Carcinoma 1 Adenocarcinoma In-situ 2 HSIL/AGUS 1 ASC-H/ASC-US	7 Glandular Carcinoma 1 Squamous Cell Carcinoma 1 AGUS 1 HSIL
1 Adenocarcinoma In-Situ	1 Adenocarcinoma In-Situ	1 Adenocarcinoma In- Situ
22 Squamous Cell Carcinoma	3 Glandular Carcinoma 12 Squamous Cell Carcinoma 1 Squamous/Glandular Carcinoma 2 Adenocarcinoma In-Situ 4 HSIL	21 Squamous Cell Carcinoma 1 Adenocarcinoma In-Situ
Total = 33	Total = 33	Total = 33

*In the intended use of the ThinPrep Imaging System, the Cytotechnologist would perform a full slide review of each of these cases and pass them on to a Cytopathologist for further review.
**In the intended use of the ThinPrep Imaging System, the Cytopathologist would perform a full manual review of each of these cases.

In 33 of the 33 cases TIS identified and presented diagnostic cells in the 22 fields of view that were indicative of cancer or its precursor lesion. In two slides (of the 33 cases) that did not contain cancer cells in the 22 fields of view, 45 HSIL cells on one slide and 17 AGUS cells on the other slide were presented. For each of the 33 cases mentioned above, the Autoscan mode of the ThinPrep Imaging System would be required to manually screen the entire ThinPrep slide. These study results demonstrate that the ThinPrep Imaging System-assisted review of the 22 fields of view will accurately lead to a full manual slide review for the detection of cervical cancer or its precursor lesions.

3. Abnormal Cell Field-of-View Reproducibility Study

The objective of this study was to validate the effectiveness of the ThinPrep Imaging

System in obtaining a reproducible number of fields of view that contain one or more abnormal cells in the 22 selected fields by performing multiple imaging and cytotechnologist review cycles on the same set of slides. The study design consisted of a set of 50 Thin Prep slides with abnormal diagnoses that were prepared on the TP-2000 or TP-3000 instruments and processed on one ThinPrep Imaging System five (5) consecutive times. A cytotechnologist used the Review Scope to review the slides recording the most abnormal cell type in each of the 22 fields of view. Abnormality was defined as any abnormal object according to Bethesda System 2001 criteria of any diagnostic level that would be noted by the cytotechnologist to trigger a full slide review. No additional review of the slide beyond the 22 fields was allowed and no movement outside each field-of-view was allowed. To reduce recognition bias of any of the fields of view from a previous screened slide, the cytotechnologist waited two (2) days between each screening cycle.

The range of abnormal fields of view presented to the cytotechnologist was 4 to 22 with a mean of 18.9 fields. Linear regression analysis over multiple imaging and review cycles yielded a correlation cofficient of 0.86 indicating good correlation. In clinical use, the cytotechnologist would be required to use the Autoscan mode of the Review Scope and thoroughly screen any slide when one field-of-view is presented that contains an abnormal cell.

4. Inter-Instrument Reproducibility Study

The objective of this study was to demonstrate that multiple reviews of the same slide set by the same cytotechnologist on three ThinPrep Imaging System instruments would produce similar diagnoses of the slides as evaluated by cytologic diagnoses and specimen adequacy. The study design was a prospective, single-blinded approach based on a review of a set of 100 negative and abnormal ThinPrep slides. A one-week interval between screening was required to minimize recognition bias. Eight of the 100 slides could not be processed on the imager for at least one of the imaging runs, and were excluded, leaving 92 slides. From the 92 slides, 4 slides yielded an unsatisfactory specimen adequacy diagnosis from at least 1 cytotechnologist screening. Since there was no descriptive diagnosis for these unsatisfactory slides, they were excluded leaving 88 slides in the study.

Comparison of descriptive diagnoses and specimen adequacy results from a single ThinPrep slide when screened with three different ThinPrep Imaging Systems yielded the following results. The Kappa statistic showed good agreement for descriptive diagnostic reproducibility with a Kappa of 0.87 with a 95% confidence interval of 0.76 to 0.98. The data also show there is consistent agreement for specimen adequacy reproducibility among the three ThinPrep Imaging System instruments. Because the data were concentrated in one category (Satisfactory), the Kappa statistic was not determined.

5. Intra-Instrument Reproducibility Study

The objective of this study was to demonstrate that an identical slide set processed multiple times and reviewed by the same cytotechnologist on one ThinPrep Imaging System instrument would produce similar diagnoses of the slides as evaluated by cytologic diagnoses and specimen adequacy. The study design was a prospective,

single-blinded two-arm approach based on a review of 100 negative and abnormal ThinPrep slides. A one-week interval between screening was required to minimize recognition bias. Eleven of the 100 slides could not be processed on the imager for at least one of the imaging runs and were excluded, leaving 89 slides. From the 89 slides, 2 slides yielded an Unsatisfactory specimen adequacy result from at least 1 cytotechnologist screening. Since there was no descriptive diagnosis for these unsatisfactory slides, they were excluded leaving 87 slides in the study.

The comparison of descriptive diagnoses and specimen adequacy results from a single ThinPrep slide, when screened three times on the same ThinPrep Imaging System by the same cytotechnologist yielded the following results. The Kappa statistic showed good agreement for descriptive diagnostic reproducibility with a Kappa of 0.85 with a 95% confidence interval of 0.76 to 0.94. The data show consistent agreement for specimen adequacy reproducibility as there was disagreement for only 2 out 89 slides. Because the data were concentrated in one category (Satisfactory), the Kappa statistic was not determined.

6. Inter-Review Scope Reproducibility Study

The purpose of this study was to evaluate the reproducibility of one ThinPrep Imaging System -assisted screening of ThinPrep slides using one cytotechnologist and multiple Review Scopes when comparing cytologic diagnoses and specimen adequacy. The study design was a prospective, single-blinded two-arm approach based on a review of 100 negative and abnormal ThinPrep slides. A one-week interval between screening was required to minimize recognition bias. Three of the 100 slides could not be processed on the Imager for at least one of the imaging runs and were excluded, leaving 97 slides. From the 97 slides, 2 yielded an Unsatisfactory specimen adequacy result from at least 1 cytotechnologist screening. Since there was no descriptive diagnosis for these unsatisfactory slides, they were excluded leaving 95 slides in the study.

The comparison of descriptive diagnoses and specimen adequacy from a single ThinPrep slide, when screened using three different Review Scopes yielded the following results. The Kappa statistic showed good agreement for descriptive diagnostic reproducibility with a Kappa of 0.80 with a 95% confidence interval of 0.70 to 0.89 indicating agreement among the three Review Scopes. The data show consistent agreement for specimen adequacy reproducibility as there was disagreement for only 1 out 95 slides. Because the data were concentrated in one category (Satisfactory), the Kappa statistic was not determined.

7. Inter-Cytotechnologist Reproducibility Study

The purpose of this was to evaluate the reproducibility (variability) of ThinPrep Imaging System-assisted screening of Thin Prep slides by three different cytotechnologists for cytologic diagnosis and specimen adequacy is similar to results obtained by manual screening. This two-arm approach was used to review 100 negative and abnormal slides. Three of the 100 slides could not be processed on the Imager for at least one of the imaging runs, and were excluded, leaving 97 slides. From the 97 slides, 4 yielded an Unsatisfactory specimen adequacy from at least 1 cytotechnologist screening. Since there was no descriptive diagnosis for these

unsatisfactory slides, they were excluded leaving 93 slides in the study.

This study yielded the following results. The Kappa statistic showed agreement for the Descriptive Diagnosis-Manual with a Kappa of 0.72 with a 95% confidence interval of 0.63 to 0.81. The Kappa statistic showed agreement for the Descriptive Diagnosis-ThinPrep Imaging System with a Kappa of 0.69 with a 95% confidence interval of 0.60 to 0.79. The 95% confidence intervals overlap between the two methods indicating there is similar variability when diagnoses are obtained by either of these two methods. The data show consistent agreement for specimen adequacy between the cytotechnologists for both manual and the ThinPrep Imaging System-assisted screening.

8. Unsatisfactory Slide Study

The purpose of the study was to evaluate the discordant unsatisfactory slides from the ThinPrep Imaging System-201 clinical trial to see if different methods of determining the numbers of squamous epithelial cells on a slide would produce different results. ThinPrep slides that produced discordant Unsatisfactory results (manual arm vs. Imager Review arm) during the clinical trial were evaluated in the following manner. Initial screening by a cytotechnologist determined descriptive diagnosis and specimen adequacy according to the Bethesda System 1991 criteria applied to the 22 fields of view; then cell count estimates were performed on the slides by four additional methods:

(1) Manual assessment of specimen adequacy on the entire microscope slide based on ThinPrep Bethesda System 1991 criteria.
(2) A cell count estimate and specimen adequacy determination made using the "diameter" method of Bethesda 2001 that recommends counting cells in 10 fields of view along the diameter of cell spot and calculating the number of cells on the slide.
(3) A cell count estimate and specimen adequacy determination made by counting the number of cells in the 22 fields located by the ThinPrep Imaging System and calculating the number of cells on the slide.
(4) A cell count estimate and specimen adequacy determination made based on cell counts from one-half the area of the cell spot and calculating the number of cells on the slide.

The Control Method for this study was a cell count and specimen adequacy based on cell counts performed on one half of the area of the slide using a rectangle in a checkerboard pattern. The total number of cells was doubled to get an estimate of the total cells on the slide. This count was used as a comparison for the other test methods. There were 67 unsatisfactory slides available from the manual review arm of the clinical trial, and 30 from the Imager Review arm. Nineteen slides were unsatisfactory on both arms (concordant) and were removed from this study leaving 59 slides [(67-19)+ (30-19)]. One of the 59 slides could not be located leaving 58 in the study.

This study yielded the following results. The specimen adequacy results for both (test) cell counting methods (Imager Review-assisted Bethesda 2001 and Bethesda 2001) are consistent with the Half-slide (control) cell count. The specimen adequacy results generated by ThinPrep Imaging System-assisted Bethesda 2001 and Bethesda 2001 are similar. The specimen adequacy results generated in the ThinPrep Imaging System-201 clinical trial for these slides are significantly different than specimen adequacy results based on the Half-Slide (control) cell count. The overall specimen adequacy determinations using Bethesda 1991 criteria do not agree well with the overall Bethesda 2001 (cell count) specimen adequacy methods. As a result of this study demonstrating that the specimen adequacy determinations using the Bethesda 1991 criteria do not agree with the other methods, Cytyc will recommend using either the Bethesda 2001 "diameter cell count" method or the cell count from each of the 22 fields of view for determining the cellular component of the adequacy assessment.

9. Slide Coverslip Movement Study

In response to concerns about coverslip movement and subsequent misalignment of the slide on the microscope, a study was conducted to measure a range of forces that a slide coverslip could be exposed to during normal and aggressive handling, and to measure the forces required to cause movement at various times during the drying process. The key variables investigated were drying time, temperature of the coverslip adhesives, and the forces that may be applied to the coverslip.

In the Handling Force Study, bench testing using a mounted slide and a force gauge was used to measure various handling forces such as normal handling (finger pressure with rubber gloves); three-pass cleaning motion sweep using xylene cleaning solution; aggressive handling using finger pressure with rubber gloves; and over-aggressive

handling with maximum finger pressure in rubber gloves. The first three methods of handling the slide indicate a progression of forces which are at 8.10 oz or below, with normal handling at 4.5 oz. These are the ranges likely to be encountered in routine slide handling.

In the Adhesion Study, bench testing was performed to establish the force required to cause coverslip motion for various drying times and temperatures. Drying times tested were 1, 2, 3, and 6 hours in the oven at 37^0C and 12 hours (overnight) at 37^0C and room temperature. Results show that oven drying at 37^0C for 2 hours or more will yield bond strength of 12.52 oz. that is above the normal expected handling forces. Overnight (12 hours) drying time at room temperature yields similar bond strength. Both of these studies indicate that when the instructions on required drying time and temperature are adhered to, the potential for coverslip movement and cell migration will not occur when the slide is exposed to normal handling conditions.

X. SUMMARY OF CLINICAL STUDIES

Objectives of the Clinical Studies.
Two clinical investigations were submitted by Cytyc. The objectives of both of the clinical studies were to assess the safety and effectiveness of the ThinPrep Imaging System in assisting in primary cervical cancer screening of ThinPrep Pap Test slides for the presence of atypical cells, cervical neoplasia, including its precursor lesions (Low Grade Squamous Intraepithelial Lesions, High Grade Squamous Intraepithelial Lesions), and carcinoma as well as all other cytologic criteria as defined by 2001 Bethesda System: Terminology for Reporting Results of Cervical Cytology.

1. Clinical Study 201

a. Study Design

The clinical trial was designed to establish that routine screening of ThinPrep Pap Test slides using the ThinPrep Imaging System was equivalent to the manual microscopic review of ThinPrep slides for all categories used for cytological diagnosis (specimen adequacy and descriptive diagnosis) as defined by the Bethesda System. The clinical trial was a multi-center, prospective, matched-pair, two arm approach in which a test and control cytology review were performed on a single ThinPrep slide. A single slide from each specimen was prepared on a ThinPrep system and stained with the Cytyc ThinPrep Stain. In the control arm of the study, the slide was manually reviewed slide using standard microscope and routine laboratory cervical cytology practices. In the test arm of the study, the same slide was re-reviewed using the ThinPrep Imaging System. In order to eliminate the potential for inter-reviewer bias, the same cytotechnologist reviewed the same slide for a given case in both study arms. If the slide was referred to the site pathologist for review, the same pathologist reviewed the same slide in both study arms. To minimize review (recognition) bias, the cytotechnologists/pathologists evaluating ThinPrep Imaging System arm slides were masked to the initial manual screening diagnosis and a minimum of a 48-day time lag or washout period was required between the manual and the Imager review. In addition, the order in which the slides

were presented to the cytotechnologist for review was different in each arm of the study.

The slides from all discordant cases (one-grade or higher cytologic difference for descriptive diagnosis) were reviewed and adjudicated by a panel of three (3) independent pathologists to determine a consensus diagnosis. Along with the discordant cases, all positive concordant cases and 5% of the negative concordant cases were adjudicated also. The adjudication pathologists were masked to the original diagnosis and the slides were presented in a randomized manner. A consensus diagnosis required agreement by at least 2 of the 3 pathologists. If a consensus diagnosis was not obtained, then the slide was reviewed at a multi-headed microscope by the same 3 pathologists for agreement.

b. Study Sites

The multi-center trial was conducted at four sites: BayState Medical Center, Springfield, MA, (Bruce Dziura, M.D., Principal Investigator); Cleveland Clinic Foundation, Cleveland, OH, (Charles Biscotti, M.D., Principal Investigator); Quest Diagnostics, Inc., Cambridge, MA, (Salim Kabawat, M.D., Principal Investigator); and South Bend Medical Foundation, South Bend, IN, (Luis Galup, M.D., Principal Investigator).

Table 2. Study Site Demographics

Site	1	2	3	4
Low Risk Population	88%	82%	90%	94%
High Risk Population	12%	18%	10%	6%
HSIL+ prevalence	1.1%	0.7%	0.4%	0.6%
ThinPreps Pap Tests Per Year	120,000	70,200	280,000	105,000
Number of Cytotechnologists	14	9	32	11
Number of Cytotechnologists in Study	2	2	2	2
Number of Cytopathologists	6	5	6	14
Number of Cytopathologists in Study	1	2	1	2

c. Study Population

Subject Selection and Criteria

The specimens included in the study were from residual ThinPrep Pap Tests collected at each study site and included women being routinely screened and women with a recent previous cervical abnormality (referral population). There is no gender bias issue involved as the Pap Test is for women only.

Inclusion criteria: all ThinPrep Pap specimens received at the clinical sites from women receiving a test for routine screening or as a follow-up to a previous abnormal Pap test.

Exclusion criteria: (1) ThinPrep specimens from which a slide could not be made because they contained too little residual specimen and (2) ThinPrep specimens not processed within the three (3) weeks of original specimen collection.

Table 3. Sample Collection Dates

Site	1	2	3	4
Duration of Study	02/02/01 – 10/18/01	02/23/01 – 10/01/01	05/08/01 – 10/31/01	12/12/00 - 8/17/01
Dates of Sample Collection	02/02/01 - 04/04/01	02/23/01 – 05/08/01	05/08/01 – 07/03/01	12/12/00 – 02/01/01

Sample Size

The following table summarizes the number of subjects projected in the protocol for each study site and the number of subjects actually entered into the study.

Table 4. Projected versus Actual Number of Subjects entered into the Clinical Study

Site	Required Number	Targeted Number	Actual Number
1	2500	2576	2584
2	2500	2690	2691
3	2500	2696	2847
4	2500	2620	2620
TOTAL	10,000	10,582	10,742

A total of 10,742 patients ranging in age from 13 to 93 years were entered into the study; 1115 could not be evaluated and 77 were excluded because of inadequate specimen (UNSAT) leaving 9,550 patients in the primary data analysis. Of the 1115 patients that could not be evaluated, 383 were due to study related errors while 732 (7.1%) could not be processed on the ThinPrep Imaging System instrument. See Table 5 below.

Table 5. Total Number of Evaluable Subjects Entered into the Clinical Study

SITE	Specimens Included	Specimens Excluded - Study Related Issues	Evaluable Specimens Not Read by ThinPrep Imaging System	Evaluable Specimens Read by ThinPrep Imaging System
1	2584	15	256	2313
2	2691	63	146	2482
3	2847	293	226	2328
4	2620	12	104	2505
TOTAL	10,742	383	732	9627

Following exclusion of 383 cases for study related issues; an additional 732 cases were removed from the statistical assessments of the clinical data due to the fact that

they could not be read on the ThinPrep Imaging System. Therefore a Manual Review occurred on both study arms for these cases and they are excluded from the study analysis tables. Of the remaining 9,627 cases, 77 cases were removed from the descriptive diagnosis assessments due to an unsatisfactory specimen adequacy result on either, or both, study arms. Therefore, the unadjudicated descriptive diagnosis tables are based on 9,550 cases.

d. Unadjudicated Descriptive Diagnosis Data

The major diagnostic categories of the Bethesda System were used to examine the agreement between the manual review and the ThinPrep Imaging System-assisted review findings for the unadjudicated data. Table 6 below shows the unadjudicated descriptive diagnosis from all four sites combined for each method of review.

Table 6. Unadjudicated 7 x 7 Classification Table for All Sites

		Imager Review							
		NEG	ASCUS	AGUS	LSIL	HSIL	SQ CA	GL CA	TOTAL
Manual Review	Neg	8550	215	8	24	6	0	1	8804
	ASCUS	176	108	0	46	7	0	0	337
	AGUS	7	4	1	0	1	0	0	13
	LSIL	29	45	0	145	19	0	0	238
	HSIL	12	6	0	26	105	2	0	151
	SQ CA	0	0	0	0	2	1	0	3
	GL CA	2	0	1	0	0	0	1	4
	TOTAL	8776	378	10	241	140	3	2	9550

Abbreviations for Diagnoses: NEG = Normal or negative, ASCUS = Atypical Squamous Cells of Undetermined Significance, AGUS = Atypical Glandular Cells of Undetermined Significance, LSIL = Low-grade Squamous Intraepithelial Lesion, HSIL = High-grade Squamous Intraepithelial Lesion, SQ CA = Squamous Cell Carcinoma, GL CA = Glandular Cell Adenocarcinoma.

e. Adjudicated Descriptive Diagnosis Data

A panel of three independent expert cytopathologists adjudicated slides from all cases with a one-grade or higher cytologic difference for descriptive diagnosis. In addition, 100 % of the positive (abnormal) concordant cases and 5% of the negative concordant cases were adjudicated. The adjudicated cases were used to establish a consensus (truth) diagnosis. The following 6x6 tables show the performance of the Imager Review versus the Manual Review compared to the final consensus diagnosis as determined by the adjudication panel (truth) for the major descriptive diagnosis classes of the Bethesda System: Negative; ASCUS; AGUS; LSIL; HSIL and CA (includes squamous cell and glandular cancer).

Table 7. 6x6 'True Negative" Contingency Table, All Sites Combined

All 786 Cases Determined To Be Negative By Adjudication

Unadjudicated Imager Review Arm Diagnosis	Unadjudicated Manual Review Arm Diagnosis						
	NEG	ASCUS	AGUS	LSIL	HSIL	CA	TOTAL
NEG	425	138	6	10	6	2	587
ASCUS	130	39	1	3	-	-	173
AGUS	5	-	-	-	-	-	5
LSIL	9	5	-	2	-	-	16
HSIL	1	1	-	-	3	-	5
CA	-	-	-	-	-	-	0
TOTAL	570	183	7	15	9	2	786

Among the 786 cases determined by the adjudication panel to be Negative, 587 (74.7%) cases in the Imager Review arm and 570 (72.5%) cases in the Manual Review arm were diagnosed as Negative and 21 (2.7%) cases in the Imager Review arm and 26 (3.3%) cases in the Manual Review arm were diagnosed as LSIL+.

Table 8. 6x6 "True ASCUS" Contingency Table, All Sites Combined

All 251 Cases Determined To Be ASCUS By Adjudication

Unadjudicated Imager Review Arm Diagnosis	Unadjudicated Manual Review Arm Diagnosis						
	NEG	ASCUS	AGUS	LSIL	HSIL	CA	TOTAL
NEG	3	32	-	7	3	-	45
ASCUS	70	47	1	20	4	-	142
AGUS	1	-	-	-	-	-	2
LSIL	6	21	-	16	7	-	50
HSIL	2	3	-	5	1	1	12
CA	1	-	-	-	-	-	1
TOTAL	83	103	1	48	15	1	251

Among the 251 cases determined by the adjudication panel to be ASCUS, 142 (56.6%) cases in the Imager Review arm and 103 (41.0%) cases in the Manual Review arm were diagnosed as ASCUS and 45 (17.9%) cases in the Imager Review arm and 83 (33.1%) cases in the Manual Review arm were diagnosed as Negative.

Table 9. 6x6 “True AGUS” Contingency Table, All Sites Combined

All 10 Cases Determined To Be AGUS By Adjudication

Unadjudicated Imager Review Arm Diagnosis	Unadjudicated Manual Review Arm Diagnosis						
	NEG	ASCUS	AGUS	LSIL	HSIL	CA	TOTAL
NEG	-	2	1	-	1	-	4
ASCUS	-	-	1	-	-	-	1
AGUS	2	-	1	-	-	1	4
LSIL	-	-	-	-	-	-	0
HSIL	-	-	-	-	-	-	0
CA	-	-	-	-	-	1	1
TOTAL	2	2	3	0	1	2	10

Among the 10 cases determined by the adjudication panel to be AGUS, 4 (40.0%) cases in the Imager Review arm and 3 (30.0%) cases in the Manual Review arm were diagnosed as AGUS and 4 (40.0%) cases in the Imager Review arm and 2 (20.0%) cases in the Manual Review arm were diagnosed as Negative.

Table 10. 6x6 “True LSIL” Contingency Table, All Sites Combined

All 236 Cases Determined To Be LSIL By Adjudication

Unadjudicated Imager Review Arm Diagnosis	Unadjudicated Manual Review Arm Diagnosis						
	NEG	ASCUS	AGUS	LSIL	HSIL	CA	TOTAL
NEG	-	4	-	12	1	-	17
ASCUS	13	16	-	20	1	-	50
AGUS	-	-	-	-	-	-	0
LSIL	8	20	-	115	12	-	155
HSIL	-	-	-	5	9	-	14
CA	-	-	-	-	-	-	0
TOTAL	21	40	0	152	23	0	236

Among the 236 cases determined by the adjudication panel to be LSIL, 155 (65.6%) cases in the Imager Review arm and 152 (64.4%) cases in the Manual Review arm were diagnosed as LSIL and 17 (7.2%) cases in the Imager Review arm and 21 (8.9%) cases in the Manual Review arm were diagnosed as Negative.

Table 11. 6x6 “True HSIL” Contingency Table, All Sites Combined

All 138 Cases Determined To Be HSIL By Adjudication

Unadjudicated Imager Review Arm Diagnosis	Unadjudicated Manual Review Arm Diagnosis						
	NEG	ASCUS	AGUS	LSIL	HSIL	CA	TOTAL
NEG	-	1	-	-	1	-	2
ASCUS	2	4	-	2	1	-	9
AGUS	-	-	-	-	-	-	0
LSIL	1	-	-	10	6	-	17
HSIL	3	3	1	9	91	1	108
CA	-	-	-	-	1	1	2
TOTAL	6	8	1	21	100	2	138

Among the 138 cases determined by the adjudication panel to be HSIL, 108 (78.3%) cases in the Imager Review arm and 100 (72.5%) cases in the Manual Review arm were diagnosed as HSIL and 2 (1.4%) cases in the Imager Review arm and 6 (4.3%) cases in the Manual Review arm were diagnosed as Negative.

"True Squamous Cell Cancer"
There was one (1) squamous cell carcinoma (SQ CA) case resulting from adjudication. It was diagnosed as HSIL in the Imager Review arm and SQ CA in the Manual Review arm.

f. Sensitivity/Specificity Tables for Descriptive Diagnoses Categories
The following tables summarize the descriptive diagnosis sensitivity and specificity estimates with 95% confidence intervals for each of the four sites and all sites combined for "true" ASCUS+, LSIL+, and HSIL+.

Table 12. Adjudicated Review versus Imager and Manual Review, ASCUS+ Descriptive Diagnosis Summary.

Sensitivity is a percent of "true" ASCUS+ (combined ASCUS, AGUS, LSIL, HSIL, SQ CA, and GL CA) slides classified in either study arm as ASCUS+ and specificity is a percent of "true" Negative slides classified in either study arm as Negative.

Sensitivity				Specificity			
Site/ #Cases	Manual	Imager	Difference	Site/ #Cases	Manual	Imager	Difference
Site 1 180	77.2% (70.4, 83.1)	78.3% (71.6, 84.1)	+1.1% (-5.8, 8.0)	Site 1 2132	98.7% (98.1, 99.1)	99.2% (98.7, 99.5)	+0.4% (-0.1, 1.0)
Site 2 230	63.1% (56.5, 69.3)	77.5% (71.4, 82.6)	+14.4% (8.2, 20.5)	Site 2 2210	95.8% (94.9, 96.6)	96.1% (95.2, 96.9)	+0.3% (-0.7, 1.3)
Site 3 103	80.6% (71.6, 87.7)	94.2% (87.8, 97.8)	+13.6% (4.3, 22.9)	Site 3 2196	98.5% (97.9, 99.0)	98.8% (98..3, 99..2)	+0.4% (-0.3, 1.0)
Site 4 179	87.2% (81.4, 91.7)	84.4% (78.2, 89.4)	-2.8% (-10.6, 5.0)	Site 4 2313	97.3% (96.6, 97.9)	97.0% (96.2, 97.7)	-0.3% (-1.1, 0.5)
All 692	75.6% (72.2, 78.8)	82.0% (78.8, 84.8)	+6.4% (2.6, 10.0)	All 8851	97.6% (97.2, 97.9)	97.7% (97.4, 98.0)	+0.2% (-0.2, 0.6)

Numbers in parentheses represent 95% confidence intervals; # = number of cases.

The results presented in Table 12 show that for ASCUS+, the increase in sensitivity of the Imager Review over the Manual Review was statistically significant with the lower limit of the 95% confidence interval being 2.6% for all sites combined. The observed difference between sensitivities for ASCUS+ varied among the sites from –2.8% with a 95% confidence interval of (–10.6%; 5.0%) to +14.4% with a 95% confidence interval of (8.2%; 20.5%). The difference in specificity results between the Imager Review and the Manual Review was not statistically significant with a 95% confidence interval of -0.2% to +0.6%. The observed differences between specificities varied among the sites from –0.3% to +0.4%.

Table 13. Adjudicated Review versus Imager and Manual Review, LSIL+ Descriptive Diagnosis Summary for Each Site and All Sites Combined.

Sensitivity is a percent of "true" LSIL+ (combined LSIL, HSIL, SQ CA, and GL CA) slides classified in either study arm as HSIL+ and specificity is a percent of "true" not LSIL+ (combined Negative, ASCUS, AGUS) slides classified in either study arm as not LSIL+.

Sensitivity				Specificity			
Site/ #Cases	Manual	Imager	Difference	Site/ #Cases	Manual	Imager	Difference
Site 1	**84.6%**	**82.7%**	**-1.9%**	Site 1	**98.7%**	**99.3%**	**+0.6%**
104	(76.2, 90.9)	(74.0, 89.4)	(-9.5, 5.6)	2208	(98.1, 99.1)	(98.9, 99.6)	(0.1, 1.0)
Site 2	**70.4%**	**72.4%**	**+2.0%**	Site 2	**99.3%**	**98.9%**	**-0.4%**
98	(60.3, 79.2)	(62.5, 81.0)	(-6.9, 11.0)	2342	(98.8, 99.6)	(98.4, 99.3)	(-0.8, .001)
Site 3	**77.4%**	**85.5%**	**+8.1%**	Site 3	**99.2%**	**99.5%**	**+0.3%**
62	(65.0, 87.1)	(74.2, 93.1)	(-4.0, 20.1)	2237	(98.7, 99.5)	(99.1, 99.8)	(-0.1, 0.6)
Site 4	**84.7%**	**78.4%**	**-6.3%**	Site 4	**98.7%**	**98.7%**	**-0.08%**
111	(98.1, 99.1)	(76.6, 90.8)	(-14.7, 2.1)	2381	(98.2, .99.2)	(98.1, 99.1)	(-0.6, 0.4)
All	**79.7%**	**79.2%**	**-0.5%**	All	**98.9%**	**99.1%**	**+0.09%**
375	(75.3, 83.7)	(74.7, 83.2)	(-5.0, 4.0)	9168	(98.8, 99.2)	(98.9, 99.3)	(-0.1, 0.3)

Numbers in parentheses represent 95% confidence intervals; # = number of cases.

The results presented in Table 13 show that the difference between sensitivities of the Imager Review and Manual Review arms for LSIL+ for all sites combined was not statistically significant with a 95% confidence interval of –5.0% to +4.0%. The observed difference between sensitivities for LSIL+ varied among the sites from –6.3% with a 95% confidence interval of (–14.7%; 2.1%) to +8.1% with a 95% confidence interval of (–4.0%; 20.1%). The difference in specificity results between the Imager Review and the Manual Review was not statistically significant with a 95% confidence interval of -0.1% to +0.3%. The observed differences between specificities varied among the sites from –0.4% to +0.6%.

Table 14. Adjudicated Review versus Imager and Manual Review, HSIL+ Descriptive Diagnosis Summary for Each Site and All Sites Combined.

Sensitivity is a percent of "true" HSIL+ (combined HSIL, SQ CA, and GL CA) slides classified in either study arm as HSIL+ and specificity is a percent of true not HSIL+ (Negative, ASCUS, AGUS, LSIL) slides classified in either study arm as not HSIL+.

Sensitivity				Specificity			
Site/ #Cases	Manual	Imager	Difference	Site/ #Cases	Manual	Imager	Difference
Site 1	89.5%	92.1%	2.6%	Site 1	98.8%	99.5%	+0.7%
38	(75.2, 97.1)	(78.6, 98.3)	(-8..9, 14..1)	2274	(98.3, 99.2)	(99.1, 99.8)	(0.2, 1.1)
Site 2	72.5%	70.0%	-2.5%	Site 2	99.8%	99.6%	-0.1%
40	(56.1, 85.4)	(53.4, 83.4)	(-15.4, 10.4)	2400	(99.5, 99.9)	(99.2, 99.8)	(-0.3, .09)
Site 3	72.7%	86.4%	+13.6%	Site 3	99.7%	99.7%	0%
22	(49.8, 89.3)	(65.1, 97.1)	(-0.7, 28.0)	2277	(99.4, 99.9)	(99.4, 99.9)	(-0.2, 0.2)
Site 4	61.5%	74.4%	+12.8%	Site 4	99.5%	99.8%	+0.3%
39	(44.6, 76.6)	(57.9, 87.0)	(-1.7, 27.4)	2453	(99.2, 99.8)	(99.5, 99.9)	(-0.003, 0.6)
All	74.1%	79.9%	+5.8%	All	99.4 %	99.6%	+0.2%
139	(66.0, 81.2)	(72.2, 86.2)	(-1.1, 12.6)	9404	(99.2, 99.6)	(99.5, 99.7)	(0.06, 0.4)

Numbers in parentheses represent 95% confidence intervals; # = number of cases.
*There was one cancer case among 140 HSIL+ cases (for performance on cancer cases, see cancer study)

The results presented in Table 14 show that the difference between sensitivities of the Imager Review and Manual Review arms for HSIL+ for all sites combined was not statistically significant with a 95% confidence interval of -1.1% to +12.6%. The observed difference between sensitivities for HSIL+ varied among the sites from –2.5% with a 95% confidence interval of (–15.4%; 10.4%) to +13.6% with a 95% confidence interval of (–0.7%; 28.0%). The increase in specificity of the Imager Review over the Manual Review was statistically significant with a 95% confidence interval of +0.06% to +0.4%. The observed differences between specificities varied among the sites from –0.1% to +0.7%.

g. Unadjudicated Marginal Frequencies Summary of Benign Cellular Changes Descriptive Diagnosis for All Sites Combined.

Table 15. Unadjudicated Marginal Frequencies Summary of Descriptive Diagnosis for Benign Cellular Changes – All Sites Combined.

	Manual Review		Imager Review	
Number of Patients:	9550		9550	
Descriptive Diagnosis	**N**	**%**	**N**	**%**
Benign Cellular Changes:	**405**	**4.2**	**293**	**3.1**
Infection:				
Trichomonas Vaginalis	8	0.1	8	0.1
Fungal organisms consistent with Candida spp.	47	0.5	31	0.3
Predominance of coccobacilli	71	0.7	60	0.6
Bacteria consistent with Actinomyces spp.	1	0.0	1	0.0
Cellular Changes associated with Herpes virus	1	0.0	1	0.0
Other Infection	1	0.0	0	0.0
Reactive Cellular Changes Associated with:				
Inflammation	218	2.3	156	1.6
Atrophic with inflammation (atrophic vaginitis)	68	0.7	46	0.5
Radiation	0	0.0	0	0.0
Intrauterine contraceptive device (IUD)	0	0.0	0	0.0
Other Reactive Cellular Change	34	0.4	14	0.1

Note: Some patients had more than one diagnostic subcategory.

h. Specimen Adequacy Study

There were 9627 subjects in the clinical study that met the requirements for inclusion in the specimen adequacy analysis. During the clinical trial, the Bethesda System 1991 criteria were used to determine the squamous cellular component for specimen adequacy and consequently the three specimen adequacies categories were recorded: Satisfactory For Evaluation (SAT), Satisfactory But Limited By (SBLB), and Unsatisfactory For Evaluation (UNSAT).

Table 16. Unadjudicated Marginal Frequencies Summary of Specimen Adequacy Results – All Sites Combined.

	Manual Review		Imager Review	
Number of Patients:	**9627**		**9627**	
Descriptive Diagnosis	**N**	**%**	**N**	**%**
Satisfactory For Evaluation	7375	76.6	7346	76.3
Satisfactory but Limited by	2186	22.7	2252	23.4
Endocervical Component Absent	1196	12.4	1397	14.5
Scant Squamous Epithelial Component	92	1.0	102	1.1
Obscuring Blood	45	0.5	17	0.2
Obscuring Inflammation	69	0.7	68	0.7
No Clinical History	982	10.2	933	9.7
Cytolysis	4	0.0	2	0.0
Other	6	0.1	33	0.3
Unsatisfactory for Evaluation	66	0.7	29	0.3
Endocervical Component Absent	6	0.1	0	0.0
Scant Squamous Epithelial Component	35	0.4	22	0.2
Obscuring Blood	17	0.2	2	0.0
Obscuring Inflammation	8	0.1	5	0.1
No Clinical History	2	0.0	2	0.0
Cytolysis	0	0.0	0	0.0
Other	2	0.0	0	0.0

Note: Some patients had more than one diagnostic subcategory.

While generally there is agreement between the Imager Review and the Manual Review for the SAT and SBLB cases, it is noted there are more UNSAT cases in the Manual Review (66) versus the Imager Review (29).

j. Adjudicated Specimen Adequacy Data

An independent pathologist adjudicated slides for specimen adequacy that were UNSAT on one study arm and SAT or SBLB on the other study arm. In addition, 100% of the UNSAT concordant cases and 5% of the SAT or SBLB concordant cases were also adjudicated. The adjudicated results were used to define the "true" specimen adequacy categories of the Bethesda System: SAT/SBLB (9569) and UNSAT (58).

Table 17. Adjudicated Review versus Imager and Manual Review, Specimen Adequacy Summary for All Sites and All Sites Combined.

Sensitivity is a percent of "true" UNSAT slides classified in either study arm as UNSAT and specificity is a percent of "true" SAT/SBLB slides classified in either study arm as SAT/SBLB.

Sensitivity				Specificity			
Site/ Number Cases	**Manual**	**Imager**	**Difference**	**Site/ Number Cases**	**Manual**	**Imager**	**Difference**
Site 1 **21**	**0%** (0/21)	**0%** (0/21)	**0.0%** (0/21)	**Site 1** **2292**	**100%** (2292/2292)	**100%** (2292/2292)	**0.0%** (0/2292)
Site 2 **6**	**100%** (6/6)	**16.7%** (1/6)	**-83.3%** (-5/6)	**Site 2** **2476**	**98.9%** (2449/2476)	**99.6%** (2465/2476)	**+0.6%** (16/2476)
Site 3 **5**	**80.0%** (4/5)	**60.0%** (3/5)	**-20.0%** (-1/5)	**Site 3** **2323**	**99.2%** (2304/2323)	**99.7%** (2315/2323)	**+0.5%** (11/2323)
Site 4 **26**	**30.8%** (8/26)	**19.2%** (5/26)	**-11.5%** (-3/26)	**Site 4** **2478**	**99.9%** (2475/2478)	**99.9%** (2476/2478)	**+0.04%** (1/2478)
All **58** **CI***	**29.3%** (17/58) (18.1, 42.7)	**13.8%** (8/58) (6.1, 25.4)	**-15.5%** (-9/58) (-25.9, -5.0)	**All** **9569** **CI***	**99.5%** (9520/9569) (99.3, 99.6)	**99.8%** (9548/9569) (99.7, 99.9)	**+0.3%** (28/9569) (0.2, 0.4)

*95% Confidence Interval

Because of the number of discordant UNSAT slides in the clinical trial, a study was performed that demonstrated that only using the Bethesda 2001 criteria for determining adequacy was appropriate. The recommended methods are (1) the Bethesda 2001 count of fields along a diagonal of the cell spot or (2) counting the cells in the 22 fields-of-view selected by the ThinPrep Imager System for determining the cellular component of the adequacy assessment.

2. Clinical Revalidation Study

After the completion of Clinical Trial 201, improvements in hardware and software were made to the ThinPrep Imaging System. All of these changes are available for review in Amendment 004. A revalidation study was initiated to ensure that all software and hardware design changes made to the device which might impact safety and effectiveness were subjected to clinical evaluation.

The design of this study was structured in a manner similar to the original Clinical Trial 201 in which the performance of the Imager Review was compared to the Manual Review. The differences were a smaller sample size; use of the Bethesda 2001 criteria for descriptive diagnoses and specimen adequacy determination; seeding of known abnormal cases; and use of a modified ThinPrep stain. There were 639 cases from low risk (asymptomatic) and high risk (symptomatic) populations and the slides were reviewed by 3 cytotechnologists.

From the 537 evaluable subjects, the adjudicated data for descriptive diagnosis and specimen adequacy demonstrated that:

- For ASCUS+, the Imager review sensitivity was 87.6% and Manual review sensitivity was 82.1%; the difference was 5.5% with 95% CI: -0.1% to 11.2%.

- For LSIL+, the Imager review sensitivity was 83.2% and Manual review sensitivity was 74.8%; the difference was 8.4% with 95% CI: 3.4% to 13.4%.

- For HSIL+, the Imager review sensitivity was 74.4% and Manual review sensitivity was 63.4%; the difference was 11.05% with 95% CI: 3.4% to 18.5%.

- The estimates of Imager specificity for ASCUS+, LSIL+, and HSIL+ were very close to the estimates of Manual specificities with low limit of 95% CI for the specificities difference about -1.5, -0.7%.

- The combined sensitivity for specimen adequacy is equivalent between the Imager review and the Manual review.

The data submitted by the sponsor demonstrated that the ThinPrep Imager System with the modifications in hardware and software described in the amendment are equivalent to the Manual review.

OST Software Review

Because of the additional improvements to the ThinPrep Imaging System which included hardware and software changes, a thorough software review was requested to verify the continued clinical performance of the Imager. The OST software reviewer states that Cytyc has provided acceptable documentation demonstrating that they have developed the software for this device under the appropriate software development program; that they have performed a hazard analysis from both the patient's and user's standpoint, and addressed those hazards; and carried out an appropriate validation process. These procedures provide the foundation for assuring, to the extent possible, that the software will operate in a manner described in the specifications, and in no other way. The Reviewer recommends that from a software standpoint this submission be approved.

X. ADDITIONAL STUDIES

Cytotechnologist Productivity Study

New technologies that find and mark the location of abnormal cells on a Pap test slide have the potential to greatly increase cytotechnologist productivity. In a Federal Register Notice (Friday January 24, 2003) the Centers for Medicare & Medicaid Services (CMS) announced the daily maximum workload limit for review of gynecologic cytology slides. This maximum number is 100 slides examined in no less

than an 8-hour workday and this limit refers to a manual review of a slide (smear and liquid-based) using a regular laboratory microscope. There is no recommendation of workload limits for automated and semi-automated screening devices. These devices are designed to allow review of a limited number of fields of view selected by the computer in order to triage the slide according to whether it is normal or abnormal. Presumably, this review using these devices will require less review time than a full manual review of the slide. Accordingly, the FR notice states that the manufacturer's instructions must be followed for pre-analytic, analytic, and post-analytic phases of testing. It is their intention that the manufacturer will state the number of slides that can be safely reviewed during the workday based on a productivity study conducted within the context of their clinical study. And in the absence of this information, the maximum workload limit for the cytotechnologists will be 100 slides examined in no less than an 8-hour day.

A guide for designing and evaluating cytotechnologists productivity studies was developed by a group of representatives from the following professional societies; American Society of Cytopathology; College of American Pathologists; International Academy of Cytology; American Society for Clinical Pathology; and Papanicolaou Society of Cytopathology. Their effort which resulted in the production of the guidance document, The Daily Workload Guidelines for Cytotechnologists Utilizing Automated Assisted-Screening Technologies was initiated at the November 2002 meeting of the Cytopathology Education and Technology Consortium (CETC) and was used to evaluate the Cytyc Productivity study.

During the course of the clinical study for the ThinPrep Imaging System, the daily cytotechnologist screening rates were recorded throughout its duration. Eight (8) cytotechnologists from the four (4) clinical sites participated in the productivity study. Their experience levels range from 5 to 23 years. The study was designed to reproduce actual clinical intended use of the ThinPrep Imager System so that the screening times for the cytotechnologists in the Imager Review arm included automated screening of the 22 fields of view with subsequent full slide review of all abnormal slides. This full slide review consists of approximately 120 fields of view. The number of hours each cytotechnologist screened slides per day varied due to logistical issues and scheduling. It is noted that with the ThinPrep Imaging System, the cytotechnologist screening rates were uniformly faster than during the Manual review.

The data tables for presenting the results from the Cytotechnologist Productivity Study are presented below:

Table 18 summarizes the cytotechnologist screening rates for both the Imager Review and the Manual Review methods. The total number of slides reviewed in the study and the average number of hours screened per day are presented for each cytotechnologist and site. Screening rates (extrapolated to an 8-hour workday) are presented as the low, average, and high daily screening rates achieved by each cytotechnologist and site. The low and high daily rates were selected for the lowest and highest daily hourly rates, respectively, and are extrapolated to 8 hours.

Table 18. Cytotechnologist Screening Rates

Site/CT	Review Methods	Total Number of Slides Evaluated	Average Number of Hours Screened Per Day	Extrapolated Daily Rates (8-hour workday)		
				Low Day	Average Day	High Day
Site 1	Manual	2568	7.4	49	69	94
	Imager	2297	6.0	107	153	206
1-1	Manual	1284	7.5	49	60	72
	Imager	1168	6.1	117	153	182
1-2	Manual	1284	7.3	70	78	94
	Imager	1129	5.9	107	154	206
Site 2	Manual	2686	7.7	40	68	80
	Imager	2665	7.8	69	109	131
2-1	Manual	1348	7.6	40	71	80
	Imager	1309	7.9	97	110	118
2-2	Manual	1338	7.8	55	66	75
	Imager	1356	7.7	69	109	131
Site 3	Manual	2738	7.9	20	80	101
	Imager	2726	4.5	148	204	320
3-1	Manual	1368	7.9	63	82	91
	Imager	1460	4.2	167	230	320
3-2	Manual	1370	7.8	20	78	101
	Imager	1266	4.7	148	178	212
Site 4	Manual	2612	7.6	42	69	94
	Imager	2524	5.1	86	138	198
4-1	Manual	1305	8.2	59	75	84
	Imager	1252	5.1	86	150	190
4-2	Manual	1307	6.9	42	63	94
	Imager	1272	5.0	109	126	198

Table 19 summarizes the Manual Review versus the Imager Review for ASCUS+ and HSIL+ sensitivity and specificity by site. The Table also summarizes the prevalence of ASCUS+, LSIL+, and HSIL+ among the reviewed slides and the respective screening daily rates of each review method. The daily screening rates of each review method are extrapolated to an 8-hour workday and are presented as the low, average, and high daily screening rates by site.

Table 19. Screening Rates, Prevalence of ASCUS+, LSIL+, HSIL+, and Respective Performance for ASCUS+ and HSIL+.

Site	% of ASCUS+	% of LSIL+	% of HSIL+	Review Methods	Extrapolated Daily Rates (8-hour workday)			Performance for ASCUS+				Performance for HSIL+			
					Low Day	Average Day	High Day	Sensitivity		Specificity		Sensitivity		Specificity	
Site 1	7.7%	4.5%	1.6%	Manual	49	69	94	77.2%	+1.1%	98.7%	+0.4%	89.5%	+2.6%	98.8%	+0.7%
				Imager	107	153	206	78.3%		99.2%		92.1%		99.5%	

Site 2	9.2%	4.0%	1.6%	Manual	40	68	80	63.1%	+14.4%	95.8%	+0.3%	72.5%	-2.5%	99.8%	-0.1%
				Imager	69	109	131	77.7%		96.1%		70.0%		99.6%	
Site 3	4.4%	2.7%	1.0%	Manual	20	80	101	80.6%	+13.6%	98.5%	+0.4%	64.3%	+13.6%	99.7%	0%
				Imager	148	204	320	94.2%		98.8%		78.6%		99.7%	
Site 4	7.2%	4.5%	1.6%	Manual	42	69	94	87.2%	-2.8%	97.3%	-0.3%	61.5%	+12.8%	99.5%	+0.3%
				Imager	86	138	198	84.4%		97.0%		74.4%		99.8%	

Based on these data, the maximum number of slides that can be reviewed when using the ThinPrep Imaging System was determined to be 200 slides in a 24-hour period. The agreed upon wording for the recommended workload maximum is as follows:

The maximum number of slides examined by an individual using the ThinPrep Imaging System should not exceed 200 slides in a 24 hour period. The maximum number of 200 slides is examined in no less than an 8-hour workday. For less than an 8-hour workday, the following formula must be applied:

(# of hours examining slide using the ThinPrep Imaging System X 200)/8

The ThinPrep Imaging System limit of 200 slides includes the following:
- **Slides where 22 Fields of View are examined**
- **Slides that require full manual review using the Autoscan feature**

The manual workload limit does not supercede the CLIA requirement of 100 slides in no less than an 8-hour day. Manual review includes the following types of slides:
- **Slides reviewed on the ThinPrep Imaging System using the Autoscan feature**
- **Slides reviewed without the ThinPrep Imaging System**
- **Non–gynecologic slides.**

When conducting manual review, refer to the CLIA requirements for calculating workload limits.

XI. CONCLUSIONS DRAWN FROM THE STUDIES

Data from the clinical and non-clinical studies demonstrate that the use of the ThinPrep Imaging System to assist in primary cervical cancer screening of ThinPrep Pap Test slides for all cytologic interpretation, as defined by the 2001 Bethesda System, is as safe and effective as the manual microscopy method of slide review.

SAFETY and EFFECTIVENESS

The clinical trial data show that for ASCUS+, the improvement in sensitivity of the Imager Review method over the Manual Review method is statistically significant with an increase of 6.4% with a 95% confidence interval of 2.6% to 10% for all sites combined. The data also demonstrated a statistically significant improvement in

specificity for HSIL+ with the Imager Review with an increase of 0.2% with a 95% confidence interval of 0.06% to 0.4% for all sites combined. For all other categories evaluated, there was no difference noted between the Imager Review and the Manual Review.

An analytical study of cancer cases demonstrated the effectiveness of the ThinPrep Imaging System in successfully identifying abnormalities in the 22 fields of view presented during the Autolocate mode of slide review. In all cases in this study, the ThinPrep Imaging System identified and presented cells among the 22 fields of view that were categorized as Cancer, HSIL, AGUS or ASCUS. Consistent with the intended use of the ThinPrep Imaging System, the cytotechnologists' diagnoses in all of these cases would have invoked the full slide Autoscan mode that would require a cytotechnologist to screen the entire slide before making a final diagnosis.

Nonclinical studies assessed reproducibility for the ThinPrep Imaging System. The linear regression analysis for the study of repeated imaging of abnormal slides resulted in a correlation coefficient of 0.86, which indicates there is good correlation in the reproducibility of the ThinPrep Imaging System when displaying fields of view that contain abnormalities.

The data from the cytotechnologist productivity study show that the screening rates achieved during the clinical trial resulted in sensitivity or specificity values that fall within acceptable limits. These results demonstrate that the increase in screening rates do not negatively impact the effectiveness of the ThinPrep Imaging System when screening ThinPrep Pap Test slides.

CDRH has concluded the device is safe and effective for its intended use.

RISK BENEFIT ANALYSIS

The results of the clinical investigation demonstrated that ThinPrep Pap Test slides reviewed with the ThinPrep Imaging System result in equivalent diagnosis to slides reviewed using the manual review method. when used with the 2001 Bethesda System: Terminology for Reporting Results of Cervical Cytology. The ThinPrep Imaging System does not contact the patient and uses slides prepared using the current method for the ThinPrep Pap Test; it therefore has minimal associated physical risks.

XII. PANEL RECOMMENDATION

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Hematology and Pathology Devices, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel. However, the Cytotechnologist Productivity Study was sent to two panel consultants as a home work assignment for their review and comment.

XIII. CDRH DECISION

CDRH issued an approval order on June 6, 2003.

The applicant's manufacturing facility was inspected on February 28, 2003 and was found to be in compliance with the device Good Manufacturing Practice regulations.

XIV. APPROVAL SPECIFICATIONS

Directions for use: See attached labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions and Adverse Events in the labeling.

Postapproval Requirements and Restrictions: See approval order.

XV. REFERENCES

1. Solomon D., Davey D, Kurman R, Moriarty A, O'Connor D, Prey M, Raab S, Sherman M, Wilbur D, Wright T, Young N, for the Forum Group Members and the 2001 Bethesda Workshop. The 2001 Bethesda System Terminology for Reporting Results of Cervical Cancer. *JAMA*. 2002;287:2114-2119

2. Kurman RJ, Solomon D. The Bethesda System for Reporting Cervical/Vaginal Cytologic Diagnoses. Springer-Verlag 1994.